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Carol L. Francis
BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025

EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/817,360	Applicant(s) GERMAN, MICHAEL S.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-11,14-17 and 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,18-21 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 12-16, 18-23, and 25-30 are pending examination.

Amendment to claims 12, 19, and 25, addition of claims 28-30, and cancellation of claim 1-11, 17, 24 in paper no. 9 is acknowledged and considered. NOTE: Applicant's request to replace the pending claims (13-16,18, 20-23, and 26-27) with the same claims in the amendment was not entered because the claims in the amendment are identical to the claim already pending.

Applicant's election without traverse of Group II and species (claim 13) in Paper No. 9 is acknowledged.

Claims 14-16 and 22-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Drawings

NOTE: In the next response, please submit a response to the PTO 948 because a PTO 948 is attached to this non-final rejection. If the reply to the Non-Final Rejection does not have a response to the PTO 948, the response will be considered non-responsive. See 37 CFR 1.85(a).

Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as

acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 18, 19, 20, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12, 18-20, and 28-30 as best understood, are readable on a genus of nucleic acid molecule encoding an islet transcription factor, wherein the genus of nucleic acid molecules is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates using a genus of nucleic acid molecule encoding an islet transcription factor for producing islet cells *in vitro*. The as-filed specification provides sufficient description of a species of transcription factors, neurogenin3 to produce α-cells. However, the state of the art displays that there are four different types of islet cells (α, β. δ, and PP-cells) with distinct phenotypes and functions. The specification does not disclose the correlation between using neurogenin3 to produce α-cells to a genus of transcription factor or combinations of transcription factors to produce the four different types of islet cells. In addition, the specification does not provide sufficient description of a representative number of nucleotide molecules encoding islet transcription factors to sufficiently describe the genus of islet transcription factors for producing the different types of islet cells. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of nucleic acid molecule encoding an islet transcription factor as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of nucleic acid molecule encoding an islet transcription factor that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of nucleic acid molecule encoding an islet transcription factor for producing islet cells *in vitro*. The

claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of nucleic acid molecule encoding an islet transcription factor for producing islet cells *in vitro* that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of nucleic acid molecule encoding an islet transcription factor for producing islet cells *in vitro* that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 12-13, 18-21, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a nucleic acid encoding the islet

transcription factor neurogenin3 operably linked to a promoter to produce glucagon producing cell from a cell *in vitro*, does not reasonably provide enablement for the full scope of the claimed invention (using a genus of islet transcription factors to differentiate a cell into any type of islet cell). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of nucleic acid molecule encoding islet transcription factor), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. producing islet cells *in vitro*.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to producing islet cells *in vitro* and using the cells in a method for producing insulin in a mammalian subject. The field of the invention lies in differentiating cells into islets cells using a nucleic acid molecule comprising an islet transcription factor.

The state of art at the time the application was filed and currently teaches that, "a number of transcription factors have been shown to control pancreas morphogenesis or the differentiation of the endocrine cells...Although no transcription factor has been identified thus far that selectively controls β-cell formation" (IDS, Schwitzgebel et al. Development, 127:5533-5540, 2000). Furthermore, research indicates that multiple factors are required for the various steps of

pancreatic cytodifferentiation. The identification of the transcription factors required for differentiation will help in understanding the timing and ultimately the signals that induce differentiation (IDS, Sander et al., J. Mol. Med. 75:327-340, 1997).

Thus, in view of the state of the art at the time the application was filed and currently, using a genus of nucleic acid molecules encoding an islet transcription factor for producing any type of islet cell *in vitro* is considered unpredictable.

The specification provides examples that will be briefly discussed herein:

Examples 1-3 are directed to isolation and production of the murine and human Ngn. Examples 4 and 15 are directed to constructing a vector encoding the murine Ngn3. Example 5 displays the induction of insulin in normal adult rats by treatment with the vector from Example 4. Examples 6, 16, and 17 display or contemplate the normalization of blood glucose levels in diabetic induced adult rats using the vector from 4 or 15. Example 7 is directed to overexpression of Ngn3 in transgenic mice. Example 8 is directed to the islet cell production in NeuroD1 transgenic mice. Examples 9 and 10 contemplate the construction of adenovirus vector comprising the human or mouse neuorD1 coding sequence or ACL1/ASH1 coding sequence and example 11 and 12 contemplate using either vector to induce the formation of insulin producing beta cells in normal adult rats. Examples 13 and 14 contemplate production of insulin in diabetic induced adult rats by the introduction of DNA encoding either neuorD1 coding sequence or ACL1/ASH1 coding sequence. Example 18 contemplates induction of the formation of islet cell in vitro. Example 19 contemplates delivery of Ngn3 to human subjects. Example 20 is characterization of the Ngn3 promoter.

The claimed invention encompasses "a method for producing an islet cell *in vitro*, the method comprising introducing a nucleic acid molecule into a cell *in vitro*, the nucleic acid molecule encoding an islet transcription factor, said introducing being in an amount sufficient for production of the islet transcription factor and production of islet cells. With respect to using a nucleic acid molecule encoding an islet transcription factor (e.g. neurogenin3) in the claimed methods, using the claimed nucleic acid molecule is not considered enabled because in view of the state of the art and the specification, a promoter is required for one skilled in the art to practice the claimed methods. The specification contemplates using an adenoviral vector for expressing the claimed transcription factors. The state of the art teaches expression of the islet transcription factor, neurogenin3 using a Pdx1 promoter (IDS, Development, 127:3533-3542, 2000). It appears from the specification that the claimed methods are only enabled for using a nucleic acid molecule operatively linked to a promoter. In view of *In re Mayhew* 527 F.2d 1229, 188 USPQ 356 (CCPA 1976), the claims are not enabled by the disclosure.

In view of the In re Wands Factors, the claimed invention is only enabled for an *in vitro* method of producing α-cells using a nucleic acid molecule encoding an islet transcription factor neurogenin3 and not the full scope of the claimed invention. The breadth of the claimed genus of nucleic acid molecules encoding an islet transcription factor is not considered enabled because the specification does not disclose how to make and use a representative number of species of transcription factors for one skilled in the art to practice the full scope of the claimed methods. The as-filed specification contemplates using several types of transcription factors and only provides sufficient guidance or factual evidence for one skilled in the art to use a transcription factor, neurogenin3, for making α-cells. Furthermore, with respect to expressing the islet

transcription factor (neurogenin3) in islet cell precursor populations, the state of the art teaches that, "the majority of cells are overwhelmingly α cells, suggesting that factors other than the bHLH factors are required" (*supra* Schwitzgebel, See Figure 10). These results suggest a model in which α-cells are the default result of neurogenein3 expression and additional signals are required to deviate neurogenin3-expressing progenitor cells to alternate cellular fates such as β cells (Figure 10). The art of record teaches that the development of the mammalian pancreas requires the concerted action of multiple transcription factors and further research is required to determine which transcription are involved in producing the four different type of islet cells (IDS, Mirmira et al, The Journal of Biological Chemistry, 275:14743-14751, 2000; Schwitzgebel et al.; Sander et al.). The working examples in the specification using neruogenin3 display that insulin producing and glucagon-producing cells were produced. However, the working examples were performed *in vivo*, so the transcription factor Ngn3 or the combination of transcription factors necessary to produce β-cells *in vitro* are not disclosed by the specification. Since that state of the art teaches that further experimentation is required to make and use the claimed genus of transcription factors and the specification lacks sufficient guidance for using the claimed genus of islet cells it would take undue amount of experimentation to practice the claimed embodiment.

Furthermore, if the applicant is able to overcome the 112 rejection set forth above for using the genus of islet transcription factors in the claimed method for producing any type of islet cell *in vitro* using any type of cell, there are concerns with respect to claims 27-29. The claimed method is only enabled for using beta cells. The specification and state of the art teach that only beta cells produce insulin and that the other three types of islet cells do not produce

insulin. It is not apparent to one skilled in the art how to make and use any islet cell to produce insulin in a mammalian subject other than beta cells. Therefore, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from using insulin producing islet cells to using non-producing insulin islet cells in a method of delivering insulin to a mammalian subject. The full scope of the claimed methods is not considered enabled.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable an *in vitro* method of producing α-cells using a nucleic acid molecule encoding an islet transcription factor neurogenin3 and not the full scope of the claimed invention. Given that differentiating any type of cell into specific islet cells was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a genus of islet transcription factors cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of differentiating cells into a specific type of cell.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 19 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 25 recites the limitation "the islet cell phenotype". There is insufficient antecedent basis for this limitation in the claim. There are four different types of islet cells with distinct phenotypes and the claims do not define the metes and bounds of the limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 12, 18, 19, 20, 28, 29, and 30 are rejected under 102(e) as being anticipated by German et al. (IDS, US Patent No. 6,127,598, 6/25/97). German teaches introducing Nkx-2.2 or Nkx6.1 encoding nucleic acid into cells to accomplish transformation of the cells and using the transformed cells to provide insulin and/or serotonin production in a subject (column 23, lines 13-50 and column 24, line 55, line 20).

Claims 12, 18, 19, 20, 28, 29, and 30 are rejected under 102(e) as being anticipated by Montminy et al. (US Patent No. 5,741,673, 8/16/93). Montminy teaches introducing a nucleic acid encoding SEQ ID NO: 2 into islet cells *in vitro* and transplanting said cells into a mammal for glucose-responsive expression of insulin (column 12, line 61-column13, line 60).

Claims 12, 18, 19, 20, 28, 29, and 30 are rejected under 102(e) as being anticipated by Habener et al. (US Patent No. 5,858,973, 2/23/94). Habener teaches producing islet cells *in vitro* by introducing a nucleic acid molecule encoding IDX-1 into cells and an *ex vivo* gene therapy method aimed at manipulation of the development transition from pancreatic α-cells to pancreatic β-cells by providing IDX-1 ex vivo (column 5, line 54-column 6, line 3).

There is no prior art on the elected species Ngn3 and there are no allowable generic or linking claims.

Gu and Palgi are cited on the 892 to show the state of the art for using any type of cell to produce islet cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635
1/13/03